General

Guideline Title

Systemic therapy for unresectable stage III or metastatic cutaneous melanoma.

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Systemic therapy for unresectable stage III or metastatic cutaneous melanoma. Edmonton (AB): CancerControl Alberta; 2015 Aug. 14 p. (Clinical practice guideline; no. CU-012). [43 references]

Guideline Status

This is the current release of the guideline.

This guideline updates a previous version: Alberta Provincial Cutaneous Tumour Team. Systemic therapy for unresectable stage III or metastatic cutaneous melanoma. Edmonton (Alberta): CancerControl Alberta; 2013 Feb. 13 p. (Clinical practice guideline; no. CU-012). [59 references]

This guideline meets NGC's 2013 (revised) inclusion criteria.

Recommendations

Major Recommendations

Treatment should be individualized based on patient and disease specific factors as determined by the treating clinician. The treatment recommendations included below are represented in the companion Management of Cutaneous Melanoma Stage IV treatment algorithm (see the "Availability of Companion Documents" field).

For American Joint Committee on Cancer melanoma staging, please refer to Appendix A in the original guideline document.

1. Patients with unresectable stage III and stage IV cutaneous melanoma should undergo BRAF biomarker testing by a College of Physicians and Surgeons of Alberta accredited laboratory to determine whether they are candidates for a BRAF inhibitor.
    - Molecular validation should be performed using parallel testing with early access program testing kits; a reasonable number of duplicate test cases (i.e., 40 samples) should be performed.
2. First-line systemic therapy
    - BRAF-positive patients
        - Clinical trials
        - Systemic targeted therapies for patients with high volume, symptomatic disease, or who are poor candidates to receive immunotherapy with ipilimumab. Examples of therapies include the following:
            - Vemurafenib (960 mg orally, twice per day) + cobimetinib (60 mg orally, once daily for 21 days, followed by 7 days off)

        - Dabrafenib (150 mg orally, twice per day) + trametinib (2 mg orally, once daily)
    - Anti-PD-1 (programmed cell death 1) antibody for patients with low volume, asymptomatic disease
        - Pembrolizumab (2 mg/kg intravenous, every 3 weeks) *Note: This drug is not currently funded by the Alberta Health Services Drug Benefit Program*
    - Ipilimumab (3 mg/kg intravenous, every 3 weeks for 4 doses) for patients with low volume, asymptomatic disease
- BRAF-negative patients
    - Clinical trials
    - Anti-PD-1 antibody
        - Pembrolizumab (2 mg/kg intravenous, every 3 weeks) *Note: This drug is not currently funded by the Alberta Health Services Drug Benefit Program*
    - Ipilimumab (3 mg/kg intravenous, every 3 weeks for 4 doses)
    - Consider targeted therapy for a defined subtype of melanoma mutational status (e.g., for c-kit positive tumors, consider c-kit inhibitors - *Note: These drugs are not currently funded by the Alberta Health Services Drug Benefit Program*)

3. Second-line systemic therapy:
    - Patients who are intolerant or who have progressed after first-line therapy may be considered for:
        - Clinical trials
        - If targeted therapy or anti-PD-1 antibody used as first-line consider ipilimumab
        - If patient BRAF-positive and has not received or has not developed resistance to BRAF/mitogen-activated protein kinase (MEK) inhibition consider targeted therapy.
        - If ipilimumab used as first-line consider targeted therapy, anti-PD-1 antibody or re-induction with ipilimumab (if patient had a response by modified World Health Organization [WHO] or immune-related response criteria [irRC] maintained for a period of 6 months or longer)

Clinical Algorithm(s)

An algorithm titled "Algorithm for the Management of Cutaneous Melanoma Stage IV" can be found in the "Availability of Companion Documents" field.

Scope

Disease/Condition(s)

Unresectable stage III or metastatic cutaneous melanoma

Note: The guideline does not include recommendations for the management of cutaneous in-transit melanoma, uveal, mucosal, or acral melanomas.

Guideline Category

Evaluation

Management

Treatment

Clinical Specialty

Dermatology

Oncology

Pathology

Intended Users

Advanced Practice Nurses

Physician Assistants

Physicians

Guideline Objective(s)

To provide evidence-based recommendations on the medical management of unresectable stage III and metastatic melanoma

Target Population

Adults over the age of 18 years with unresectable stage III and stage IV cutaneous melanoma, without involvement of the central nervous system (CNS)

Note: Different management strategies may apply to pediatric patients. For patients with CNS metastases, the priority of treatment should typically focus on the CNS disease.

Interventions and Practices Considered

1. BRAF biomarker testing to determine if patients are candidates for a BRAF inhibitor
2. Molecular validation using parallel testing with early access program testing kits
3. First-line systemic therapy
    - BRAF-positive patients: clinical trials, vemurafenib + cobimetinib, dabrafenib + trametinib, anti-PD-1 (programmed cell death 1) antibody (e.g., pembrolizumab), ipilimumab
    - BRAF-negative patients: clinical trials, pembrolizumab, ipilimumab, targeted therapy for a defined subtype of melanoma mutational status (e.g., c-kit inhibitors)
4. Second-line systemic therapy
    - Clinical trials
    - Ipilimumab (if targeted therapy or anti-PD-1 was used in first-line)
    - Targeted therapy (if there is no developed resistance to BRAF/mitogen-activated protein kinase [MEK] inhibition)
    - Targeted therapy, anti-PD-1 or ipilimumab-re-induction (if ipilimumab was used in first-line)

Major Outcomes Considered

- Survival rates (overall, progression-free)
- Tumour progression
- Response rates (objective, overall)
- Treatment-related adverse events

Methodology

Methods Used to Collect/Select the Evidence

Hand-searches of Published Literature (Primary Sources)

Hand-searches of Published Literature (Secondary Sources)

Searches of Electronic Databases

Description of Methods Used to Collect/Select the Evidence

Research Questions

Specific research questions to be addressed by the guideline document were formulated by the guideline lead(s) and Knowledge Management (KM) Specialist using the PICO question format (Patient or Population, Intervention, Comparisons, Outcomes).

Guideline Questions

- What types of systemic therapy should be considered for patients with unresectable stage III or metastatic melanoma?
- Should patients be carefully selected; if so by what criteria?
- Which agents should be used as first-line therapy and at what dosing regimen?
- Which agents should be used as second- or third-line therapy and at what dosing regimen?

Search Strategy

Databases were searched for evidence on systemic therapy for unresectable stage III or metastatic cutaneous melanoma and citations were hand-searched to identify additional relevant studies. The initial search strategy and subsequent updates can be found in Appendix B in the original guideline document. Search terms include melanoma and specific types of systemic therapy. The 2015 update included randomized controlled trials, phase III and phase II studies with at least ten patients with advanced, unresectable melanoma. Additional key studies and abstracts were identified by working group members. The National Guidelines Clearinghouse (NGC) and individual guideline organizations were also searched for practice guidelines relevant to this topic.

The search was limited to humans and English from January 2013 to July 2015. 1613 citations were found.

Date of Search: 07-14-2015

Specific Topic Areas: Systemic therapy for advanced or metastatic melanoma

Preliminary Update Search Strategy: PubMed and MEDLINE were searched for evidence on systemic therapy for unresectable stage III or metastatic cutaneous melanoma.

Inclusion: Stage III or IV cutaneous melanoma, phase II or III studies, outcomes (overall survival, progression-free survival, tumour response)

Exclusion: Active brain metastases, uveal, mucosal, or acral melanoma, retrospective studies, phase I studies

Number of Source Documents

53 articles were included

Methods Used to Assess the Quality and Strength of the Evidence

Expert Consensus

Expert Consensus (Committee)

Rating Scheme for the Strength of the Evidence

Not applicable

Methods Used to Analyze the Evidence

Review of Published Meta-Analyses

Systematic Review with Evidence Tables

Description of the Methods Used to Analyze the Evidence

Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Evidence Tables

Evidence tables containing the first author, year of publication, patient group/stage of disease, methodology, and main outcomes of interest are assembled using the studies identified in the literature search. Existing guidelines on the topic are assessed by the KM Specialist using portions of the Appraisal of Guidelines Research and Evaluation (AGREE) II instrument (http://www.agreetrust.org) and those meeting the minimum requirements are included in the evidence document. Due to limited resources, GURU does not regularly employ the use of multiple reviewers to rank the level of evidence; rather, the methodology portion of the evidence table contains the pertinent information required for the reader to judge for himself the quality of the studies.

Methods Used to Formulate the Recommendations

Expert Consensus

Description of Methods Used to Formulate the Recommendations

Development and Revision History

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team. Members of the Alberta Provincial Cutaneous Tumour Team include medical oncologists, surgeons, dermatologists, radiation oncologists, pathologists, and nurses. Evidence was selected and reviewed by a working group comprised of members from the Alberta Provincial Cutaneous Tumour Team and a Knowledge Management (KM) Specialist from the Guideline Resource Unit (GURU). A detailed description of the methodology followed during the guideline development process can be found in the GURU Handbook (see the "Availability of Companion Documents" field).

Formulating Recommendations

The working group members formulate the guideline recommendations based on the interpretation of evidence synthesized by the KM Specialist during the planning process, blended with expert clinical interpretation of the evidence. As detailed in the GURU handbook, the working group members may decide to adopt the recommendations of another institution without any revisions, adapt the recommendations of another institution or institutions to better reflect local practices, or develop their own set of recommendations by adapting some, but not all, recommendations from different guidelines.

The degree to which a recommendation is based on expert opinion of the working group and/or the Provincial Tumour Team members is explicitly stated in the guideline recommendations. Similar to the American Society of Clinical Oncology (ASCO) methodology for formulating guideline recommendations, the GURU does not use formal rating schemes for describing the strength of the recommendations, but rather describes, in conventional and explicit language, the type and quality of the research and existing guidelines that were taken into consideration when formulating the recommendations.

Rating Scheme for the Strength of the Recommendations

Not applicable

Cost Analysis

A formal cost analysis was not performed and published analyses were not reviewed.

Method of Guideline Validation

Internal Peer Review

Description of Method of Guideline Validation

This guideline was reviewed and endorsed by the Alberta Provincial Cutaneous Tumour Team.

Guideline Review and Approval

When the draft guideline document has been completed, revised, and reviewed by the Knowledge Management (KM) Specialist and the working group members, it is sent to all members of the Provincial Tumour Team for review and comment. This step ensures that those intended to use the guideline have the opportunity to review the document and identify potential difficulties for implementation before the guideline is finalized. Depending on the size of the document, and the number of people it is sent to for review, a deadline of one to two weeks will usually be given to submit any feedback. Ideally, this review will occur prior to the annual Provincial Tumour Team meeting, and a discussion of the proposed edits will take place at the meeting. The working group members will then make final revisions to the document based on the received feedback, as appropriate. Once the guideline is finalized, it is officially endorsed by the Provincial Tumour Team Lead and the Director of Provincial Clinical Teams.

Evidence Supporting the Recommendations

Type of Evidence Supporting the Recommendations

The type of evidence supporting the recommendations is not specifically stated.

Benefits/Harms of Implementing the Guideline Recommendations

Potential Benefits

Optimal selection of systemic agents for the management of unresectable stage III or metastatic cutaneous melanoma

Potential Harms

- The most common adverse events for trametinib in the METRIC study were rash, diarrhea, and peripheral edema; events were managed with dose interruption and dose reduction.
- Combination therapy of BRAF inhibitors and mitogen-activated protein kinase (MEK) inhibitors both had similar rates of adverse events; however, more dose modifications were documented in combination group.
- In a phase III study (KEYNOTE-006), the most common events observed in the pembrolizumab groups were fatigue, diarrhea, rash and pruritus.

Qualifying Statements

Qualifying Statements

The recommendations contained in this guideline are a consensus of the Alberta Provincial Cutaneous Tumour Team and are a synthesis of currently accepted approaches to management, derived from a review of relevant scientific literature. Clinicians applying these guidelines should, in consultation with the patient, use independent medical judgment in the context of individual clinical circumstances to direct care.

Implementation of the Guideline

Description of Implementation Strategy

- Present the guideline at the local and provincial tumour team meetings and weekly rounds.
- Post the guideline on the Alberta Health Services Web site.
- Send an electronic notification of the guideline to all members of CancerControl Alberta.

Implementation Tools

Clinical Algorithm

Resources

For information about availability, see the *Availability of Companion Documents* and *Patient Resources* fields below.

Institute of Medicine (IOM) National Healthcare Quality Report Categories

IOM Care Need

Getting Better

Living with Illness

IOM Domain

Effectiveness

Identifying Information and Availability

Bibliographic Source(s)

Alberta Provincial Cutaneous Tumour Team. Systemic therapy for unresectable stage III or metastatic cutaneous melanoma. Edmonton (AB): CancerControl Alberta; 2015 Aug. 14 p. (Clinical practice guideline; no. CU-012). [43 references]

Adaptation

Not applicable: The guideline was not adapted from another source.

Date Released

2015 Aug

Guideline Developer(s)

CancerControl Alberta - State/Local Government Agency [Non-U.S.]

Source(s) of Funding

CancerControl Alberta

Guideline Committee

Alberta Provincial Cutaneous Tumour Team

Composition of Group That Authored the Guideline

Members of the Alberta Provincial Cutaneous Tumour Team include medical oncologists, surgeons, dermatologists, radiation oncologists, pathologists, and nurses.

Financial Disclosures/Conflicts of Interest

Participation of members of the Alberta Provincial Cutaneous Tumour Team in the development of this guideline has been voluntary and the authors have not been remunerated for their contributions. There was no direct industry involvement in the development or dissemination of this guideline. CancerControl Alberta recognizes that although industry support of research, education and other areas is necessary in order to advance patient care, such support may lead to potential conflicts of interest. Some members of the Alberta Provincial Cutaneous Tumour Team are involved in research funded by industry or have other such potential conflicts of interest. However, the developers of this guideline are satisfied it was developed in an unbiased manner.

Guideline Status

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This guideline meets NGC's 2013 (revised) inclusion criteria.

Guideline Availability

Available from the Alberta Health Services Web site.

Availability of Companion Documents

The following are available:

- Guideline utilization resource unit handbook. Version 2. Edmonton (AB): CancerControl Alberta; 2013 Jan. 5 p. Available from the Alberta Health Services Web site.
- Algorithm for the management of cutaneous melanoma stage IV. Edmonton (AB): CancerControl Alberta; 2015 Aug. 1 p. Available from the Alberta Health Services Web site.

In addition, the American Joint Committee on Cancer (AJCC) (7th Edition) anatomic stage groupings and the tumour, node, metastases (TNM) staging categories for cutaneous melanoma are available in Appendix A of the original guideline document.

Patient Resources

None available

NGC Status

This NGC summary was completed by ECRI Institute on December 10, 2012. The information was verified by the guideline developer on January 23, 2013. This summary was updated by ECRI Institute on April 28, 2014. The updated information was verified by the guideline developer on June 6, 2014. This summary was updated again by ECRI Institute on March 14, 2016. The updated information was verified by the guideline developer on April 4, 2016.

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